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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/381,747	09/22/99	TORMO M	UTSC:550---/

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EXAMINER	
LACOURCIERE,K	
ART UNIT	**PAPER NUMBER**
1635	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.	Applic[illegible]
09/381,747	Tormo et al.
Examiner	**Group Art Unit**
Karen A. Lacourciere	1635

☒ Responsive to communication(s) filed on *Nov 13, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-60* is/are pending in the applicat

Of the above, claim(s) *50-60* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Newly submitted claims 50-60 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 50-60 are drawn to a method of reducing the non-specific toxicity of a Bcl-2-encoding poly-nucleotide/lipid association.

The method of newly presented claims 50-60 are drawn to a different invention than the method claims originally presented. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to materially different methods with different functions and effects. For example, the method of claims 50-60 are drawn to methods which function to reduce the toxicity of a composition encoding bcl-2, whereas the originally presented methods are directed to methods of treating a disease using an antisense molecule.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 50-60 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

A substitute declaration was submitted on 11-13-00 to remedy the defect in the address of inventor Tormo, as noted in the prior Office action (mailed 07-10-00). The substitute declaration (filed 11-13-00) is not acceptable because the only inventor listed is inventor Tormo. The substitute declaration does not need to be signed by all of the inventors of the instant application to be valid (only inventor Tormo's signature is required), however, all of the inventors must be listed, otherwise the declaration is stating that inventor Tormo is the sole inventor.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-20 and 39-49 are rejected as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-30, 44, and 46 of copending Application No. 08/726,211. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the claims overlap in scope and would encompass the same methods.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-9, 21-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,855,911 in view of Evan or Green et al. or Reed et al. further in view of Tormo et al.(reference C2 on PTO form 1449, filed Feb 28, 2000)

U.S. Patent No. 5,855,911 claims generally compositions which comprise an antisense oligonucleotide, including a p-ethoxy oligonucleotide, and a neutral lipid, including phospholipids such as phosphatidylcholines and dioleoylphosphatidyl cholines.

U.S. Patent No. 5,855,911 does not claim said compositions wherein the antisense oligonucleotide is targeted to bcl-2, including the initiation codon, or wherein the antisense oligonucleotide comprises the instantly claimed SEQ ID NO:1.

Tormo et al. teach a p-ethoxy antisense oligonucleotide targeted to bcl-2, delivered using a liposome composition.

Evan teaches the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein (p 7, lines 10-29), wherein the oligonucleotide is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 15, lines 16-23). Evan teaches that the antisense oligonucleotide can be synthesized from an expression construct encoding the antisense oligonucleotide (p 18, lines 26-30) and that the expression construct is preferably delivered via a liposome (p 59, lines 6-7).

Reed teaches an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of the bcl-2 protein (p 3, lines 2-22). The antisense oligonucleotide taught by Reed is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 13, lines 2-5). Reed teaches that the antisense oligonucleotide, or a vector which expresses the antisense oligonucleotide, is preferably delivered via a liposome (p 14, lines 16-25).

The invention of instant claims 1-9 and 21-38 are an obvious species of the generic claims 1-6 of U.S. Patent No. 5,855,911. It would have been obvious to one skilled in the art at the time the invention was made to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a lipid, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone and a neutral lipid composition, including phospholipids such as phosphatidylcholines and dioleoylphosphatidyl cholines, as claimed in U.S. Patent No. 5,855,911. One skilled in the art would have been motivated to modify the antisense molecules taught by Evan, Reed or Green et al. by incorporating the p-ethoxy backbone taught by U.S. Patent No. 5,855,911 for the benefit of nuclease resistance, as taught therein, and because Tormo et al. teach modification of bcl-2 targeted antisense oligonucleotides with a p-ethoxy backbone. One skilled in the art would have been motivated to use the neutral lipid formulations and p-ethoxy backbone taught U.S. Patent No. 5,855,911 for the antisense oligonucleotide liposome compositions taught

by Evan, Reed or Green et al. because U.S. Patent No. 5,855,911 teaches that liposome formulations comprised of neutral lipids, including dioleoylphosphatidylcholine, impart improved stability and cellular uptake to antisense oligonucleotides. Therefore, it would have been prima facie obvious to one skilled in the art at the time the instant invention was made to make a composition comprising the antisense oligonucleotides targeted to bcl-2 encapsulated in a liposome, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone and liposome formulations taught by U.S. Patent No. 5,855,911.

Claim 1-9 and 21-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,042,846 in view of Evan, Reed or Green et al., further in view of Tormo et al.

U.S. Patent No.6,042,846 claims generally compositions which comprise an antisense oligonucleotide, including a p-ethoxy oligonucleotide, and a neutral lipid, including phospholipids such as phosphatidylcholines and dioleoylphosphatidyl cholines.

U.S. Patent No.6,042,846 does not claim said compositions wherein the antisense oligonucleotide is targeted to bcl-2, including the initiation codon, or wherein the antisense oligonucleotide comprises the instantly claimed SEQ ID NO:1.

Tormo et al. teach a p-ethoxy antisense oligonucleotide targeted to bcl-2, delivered using a liposome composition.

Evan teaches the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein (p 7, lines 10-29), wherein the oligonucleotide is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 15, lines 16-23). Evan teaches that the antisense oligonucleotide can be synthesized from an expression construct encoding the antisense oligonucleotide (p 18, lines 26-30) and that the expression construct is preferably delivered via a liposome (p 59, lines 6-7).

Reed teaches an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of the bcl-2 protein (p 3, lines 2-22). The antisense oligonucleotide taught by Reed is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 13, lines 2-5). Reed teaches that the antisense oligonucleotide, or a vector which expresses the antisense oligonucleotide, is preferably delivered via a liposome (p 14, lines 16-25).

The invention of instant claims 1-9 and 21-38 are an obvious species of the generic claims 1-6 of U.S. Patent No.6,042,846. It would have been obvious to one skilled in the art at the time the invention was made to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a lipid, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone and a neutral lipid composition, including phospholipids such as phosphatidylcholines and dioleoylphosphatidyl cholines, as claimed in U.S. Patent No.6,042,846. One skilled in the art would have been motivated to modify the antisense molecules taught by Evan, Reed or Green et al. by incorporating the p-ethoxy backbone taught by U.S. Patent No. 6,042,846 for the benefit of nuclease resistance, as taught therein, and because Tormo et al. teach

modification of bcl-2 targeted antisense oligonucleotides with a p-ethoxy backbone. One skilled in the art would have been motivated to use the neutral lipid formulations and p-ethoxy backbone taught U.S. Patent No.6,042,846 for the antisense oligonucleotide liposome compositions taught by Evan, Reed or Green et al. because U.S. Patent No.6,042,846 teaches that liposome formulations comprised of neutral lipids, including dioleoylphosphatidylcholine, impart improved stability and cellular uptake to antisense oligonucleotides. Therefore, it would have been prima facie obvious to one skilled in the art at the time the instant invention was made to make a composition comprising the antisense oligonucleotides targeted to bcl-2 encapsulated in a liposome, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone and liposome formulations taught by U.S. Patent No.6,042,846.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 24, 25 and 36, and dependent claims, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "said at least 8 nucleotides" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "The composition association" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 25 recites the limitation "the composition" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 36, and claims dependent on claim 36, are indefinite due to the recitation “a second, bcl-2 encoding polynucleotide”. Claim 36 is unclear because claim 36 recites a second bcl-2 encoding polynucleotide without reciting a first bcl-2 encoding polynucleotide.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-20 are maintained as rejected and new claims 39-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10-20 are drawn broadly to inhibiting any disease associated with bcl-2 by administering an antisense oligonucleotide targeted to bcl-2 in a neutral liposome composition to a cell expressing bcl-2 and bax. Claims 10-20 and 39-49 are drawn broadly to methods of treatment with any bcl-2 targeted antisense for any type of cancer cell in any organism, including human, for any neutral liposome composition.

The specification as filed provides one example wherein nude mice injected with follicular lymphoma cells were treated with a liposomal composition comprising antisense targeted to bcl-2, wherein some treated mice exhibit a reduction in proliferation of the injected lymphoma cells. Further, the specification, as filed, presents examples of in vitro (cell culture) treatment of cells using compositions which comprise a neutral liposome and bcl-2 targeted antisense wherein the viability of one cell line (Johnson follicular lymphoma) is decrease, but the viability of another bcl-2/bax expressing cell line (Raji Burkitt lymphoma cells) is not effected.

No examples are presented which demonstrate an inhibition of a disease state using compositions comprising neutral lipids and bcl-2 targeted antisense, nor is there any demonstration that the reduction of proliferation of injected lymphoma cells correlates with an effective treatment for follicular lymphoma or any other bcl-2 associated disease.

The specification indicates that in vitro treatment of cancer cells using a composition comprising a neutral lipid and antisense targeted to bcl-2 is unpredictable with respect to which cell types are responsive to treatment. The specification does not provide guidance which would allow one skilled in the art to determine what cell lines would respond in vivo, or in vitro, to a composition comprising a neutral lipid and antisense targeted to bcl-2. Further, there is no evidence provided in the instant specification that inhibition of a cancer cell line in vitro using a composition comprising a neutral lipid and an antisense molecule targeted to bcl-2 would correlate with the inhibition of a disease state in vivo.

As per Agrawal, Branch and Crooke, the *in vivo* (whole organism) application of antisense without direct evidence is a highly unpredictable endeavor due to target accessibility and delivery issues. Delivery of an antisense oligonucleotide targeted to bcl-2 in vitro using a composition comprising a neutral lipid would not provide guidance for delivery of an antisense targeted to bcl-2 in vivo using a composition comprising a neutral lipid.

The specification as filed provides only one example wherein an antisense oligonucleotide targeted to bcl-2 is used to inhibit cancer cell growth in vivo. The disclosed model uses a human follicular cell line injected into an immunosuppressed mouse. It is well known in the art that

mouse models, particularly when immunosuppressed mice are used, do not always correlate with therapeutic results in humans or other organisms (see Gura, Golden). "[M]ost drugs that work in lab animals tend to be duds in humans. The field is littered with "magic bullets" that failed....no more than 10% or 20% of agents tried in mice succeed"(see Golden). Xenograft models, human tumors in immunosuppressed mice, "don't behave like naturally occurring tumors in humans...drugs tested in xenografts appeared effective but worked poorly in humans" (see Gura, p 1041, second column). Further, "animals [xenograft mice] apparently do not handle the drugs exactly the way the human body does"(Gura). Delivery of antisense targeted to bcl-2 in a xenograft mouse would not provide guidance to deliver the same antisense oligonucleotide to a human or any other mammal. Further, the mouse model presented does not demonstrate that a disease state is inhibited using the claimed method. There is no art recognized nexus disclosed between the mouse model presented and a disease state nor is there any evidence that results obtained in the disclosed mouse model would extend to any other organism, any other cell line, any other neutral lipid composition or any other bcl-2 targeted oligonucleotide.

Prophetic examples are provided for carrying out in vivo testing and treatment, however few details are provided.

Based on the broad breadth claimed, the unpredictability of the art of antisense, the unpredictability of the claimed methods demonstrated in vitro, the lack of correlating working examples, the lack of guidance provided by the inventor with respect to in vivo inhibition of a bcl-2 associated disease it would require undue trial and error experimentation for one skilled

in the art to practice the methods of inhibiting a disease using a composition of a neutral lipid and a bcl-2 targeted antisense oligonucleotide as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-9 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green et al. each in view of Tari et al. and Tormo et al.

Evan teaches the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein (p 7, lines 10-29), wherein the oligonucleotide is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 15, lines 16-23). Evan teaches that the antisense oligonucleotide can be synthesized from an expression construct encoding the antisense oligonucleotide (p 18, lines 26-30) and that the expression construct is preferably delivered via a liposome (p 59, lines 6-7).

Reed teaches an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of the bcl-2 protein (p 3, lines 2-22). The antisense oligonucleotide taught by Reed is

preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 13, lines 2-5). Reed teaches that the antisense oligonucleotide, or a vector which expresses the antisense oligonucleotide, is preferably delivered via a liposome (p 14, lines 16-25).

Green et al. teaches antisense oligonucleotides targeted to anti-apoptotic genes, including bcl-2 (column 3, lines 51-67) wherein said antisense oligonucleotides are preferably targeted to the translation initiation codon of the target gene (column 4, lines 46-51). Green et al. teach that the antisense oligonucleotides can be encapsulated into liposomes for administration (see for example column 6, lines 60-63) may be delivered using an expression vector encoding the antisense oligonucleotide (column 6, lines 8-10).

Evan, Reed and Green et al. do not teach a liposome composed of neutral lipids, nor do they teach liposomes composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, or dioleoylphosphatidylcholine. Evan, Reed and Green et al. do not teach antisense with a p-ethoxy backbone modification.

Tari et al. teach antisense oligonucleotides encapsulated in a liposome comprised of neutral lipids, including liposomes composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, or, preferably, dioleoylphosphatidylcholine (see for example column 1, line 66- column 2, line 56).

Tormo et al. teach an antisense oligonucleotide targeted to bcl-2 with a p-ethoxy backbone modification.

It would have been obvious to one skilled in the art at the time the invention was made to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a lipid, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone, as taught by Tormo et al. using the formulations taught by Tari et al. One skilled in the art would have been motivated to modify the antisense molecules taught by Evan, Reed or Green et al. by incorporating the p-ethoxy backbone taught by Tormo et al. for the benefit of nuclease resistance, as taught by Tormo et al. One skilled in the art would have been motivated to use the neutral lipid formulations taught by Tari et al. for the antisense oligonucleotide liposome compositions taught by Evan, Reed or Green et al., modified with the p-ethoxy backbone taught by Tormo et al., because Tari et al. teach that liposome formulations comprised of neutral lipids, including dioleoylphosphatidylcholine, impart improved stability and cellular uptake to antisense oligonucleotides. Therefore, it would have been prima facie obvious to one skilled in the art at the time the instant invention was made to make a composition comprising the antisense oligonucleotides targeted to bcl-2 encapsulated in a liposome, as taught by Evan, Reed or Green et al., with a p-ethoxy backbone as taught by Tormo et al., using the liposome formulations taught by Tari et al.

Response to Arguments

Applicant's arguments filed November 13, 2000 have been fully considered but they are not persuasive.

In response to the rejection under 35 U.S.C. 112 first paragraph Applicant argues that the in vitro examples presented are taught as correlating with in vivo results and Applicant provides a declaration by inventors Tari and Lopez-Berenstein (exhibit B) which asserts that the in vitro results would correlate with in vivo results. Applicant further argues that in view of *In Re Brana* the in vitro tests and examples of testing in SCID mice, that the evidence provided in the instant specification and the declaration submitted 11-13-2000 is adequate to enable the methods of treatment claimed for any organism, including humans. Applicant further argues that the Examiner's concern with the unpredictability of delivery of antisense is unfounded because the specification presents examples of systems which may be used for delivery of antisense. Applicant argues that the mouse model presented is the best experimental model available and correlates with results in vivo. Applicant provides a declaration (Exhibit C) from Dr. Richard Ford stating that nude mice have been used in preclinical animal studies and can be predictive of results in humans. Applicant cites several articles wherein nude mouse models have been used for testing small molecules as anticancer drugs.

These arguments have not been found to be persuasive. The specific administration protocols for treating a human being with the liposomal antisense composition disclosed in the specification and disclosed are not deemed to overcome the inherent unpredictability of antisense

technology as no evidence is provided that the claimed protocol would be effective in humans for the treatment of any bcl-2 associated disease. No evidence or teaching is provided that would reasonably predict that the administration protocol used in the disclosed mouse model would relate to or predict success using the administration protocol claimed. Given the lack of success in the prior art for developing an effective administration protocol for antisense and the lack of evidence for the effectiveness of the claimed protocol, the specification is not enabled for the claimed invention. *In Re Brana* requires that the in vitro results or animal models reasonably correlate with a therapeutic utility. In the instant case, there is no evidence that the mouse model disclosed would reasonably correlate with the therapeutic results claimed. Applicant cites numerous examples wherein a mouse model may correlate with a therapeutic outcome in humans, however, these models are used to test small molecules. These models are not used to demonstrate a therapeutic effect for antisense molecules. Given the inherent unpredictability of delivery of antisense, these citations would not support the disclosed mouse model or in vitro experiments as correlating with delivery of antisense in a human. Further, there is no art recognized nexus between the disclosed mouse model and cell culture model and the effectiveness of treatment for generally any bcl-2 associated disease. The declarations provided using Johnson cells and a single liposome composition comprising one particular antisense molecule cannot provide support for the broadly written claims.

In response to the rejection under 35 U.S.C. 103 (a) Applicant argues that Tari et al. teach liposomal compositions in general and there is no motivation for the skilled artisan to use neutral liposomes and that the instant specification teaches that neutral lipids are non-toxic, which Tari et al. does not teach. Applicant asserts that the rejection under U.S.C. 103(a) is dependent a teaching by Tari et al. that neutral lipids are less toxic. Applicant provides a declaration (Exhibit D) by inventors Tari and Lopez-Berestein that demonstrates lower toxicity of neutral lipids as compared to charged lipids. Applicant argues that Tari et al. is mischaracterised as teaching the benefits of neutral lipids, but instead is teaching these benefits as general to all liposome constructs disclosed in Tari et al.

These arguments have not been found to be persuasive. Tari et al., in the general disclosure of the patented invention, states that he preferred lipids are selected from phosphatidylcholines (neutral lipids) and phophatidylserines (charged lipids) with DOPC (a neutral lipid) being a particularly preferred lipid (column 2, lines 10-14). This is an explicit teaching that a neutral lipid (DOPC) is preferred over a charged lipid (phosphatidylserine). The statement by Tari et al. that DOPC was one of the easiest lipids to handle would further be sufficient for the skilled artisan to select DOPC and DOPC was the only lipid shown to effectively deliver oligonucleotides into a cell. These factors would provide sufficient motivation for one skilled in the art to select DOPC (a neutral lipid) over the other lipid compositions disclosed. The declaration provided by Tari and Lopez-Berestein indicates that the efficacy and lack of toxicity of liposomes comprising DOPC, as compared to charged lipids, is unexpected in view of Tari et

al. The showing in the declaration that liposomes comprising 30% positively or negatively charged lipids cannot be said to be surprising in view of Tari et al. because Tari et al. never tested the DOPS containing liposomes for their effect on cells. Further, Tari et al. never teaches or suggests liposomes comprising 30% DOPS or any other charged lipid, therefore, no comparison can be made between the results shown in the declaration and the teachings of Tari et al. Finally, even if a showing that charged lipids work less well than expected was surprising in view of the teachings of Tari et al., this would demonstrate an unexpected disadvantage of what is not being claimed, rather than an advantage of what is instantly claimed. The rejection of record does not depend on a motivation that neutral lipids are less toxic than charged lipids.

Conclusion

Any rejection of record not repeated in this Office Action is considered to be withdrawn.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere

January 31, 2001

JOHN L. LeGUYADER
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